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Cost-Effectiveness of Statins for Primary Prevention in Patients Newly Diagnosed with Type 2 Diabetes in The Netherlands

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ABSTRACT

Background: Statins are lipid-lowering drugs that reduce the risk of cardiovascular events in patients with diabetes. **Objectives:** The objective of this study was to determine whether statin treatment for primary prevention in newly diagnosed type 2 diabetes is cost-effective, taking nonadherence, baseline risk, and age into account. **Methods:** A cost-effectiveness analysis was performed by using a Markov model with a time horizon of 10 years. The baseline 10-year cardiovascular risk was estimated in a Dutch population of primary prevention patients with newly diagnosed diabetes from the Groningen Initiative to Analyse Type 2 Diabetes Treatment (GIANTT) database, using the United Kingdom Prospective Diabetes Study risk engine. Statin adherence was measured as pill days covered in the IADB.nl pharmacy research database. Cost-effectiveness was measured in costs per quality-adjusted life-year (QALY) from the health care payers' perspective. **Results:** For an average patient aged 60 years, the base case, statin treatment was highly cost-effective at €2245 per QALY. Favorable cost-effectiveness was robust in sensitivity analysis. Differences in age and 10-year cardiovascular risk showed large differences in cost-effectiveness from almost €100,000 per QALY to almost being cost saving. Treating all patients younger than 45 years at diabetes diagnosis was not cost-effective (weighted cost-effectiveness of almost €60,000 per QALY). **Conclusions:** Despite the nonadherence levels observed in actual practice, statin treatment is cost-effective for primary prevention in patients newly diagnosed with type 2 diabetes. Because of large differences in cost-effectiveness according to different risk and age groups, the efficiency of the treatment could be increased by targeting patients with relatively higher cardiovascular risk and higher ages.

Keywords: cardiovascular risk management, cost-effectiveness, statins, type 2 diabetes.

Introduction

The prevalence of diabetes is growing in The Netherlands, as in many countries worldwide, because of aging of the population and the occurrence of diabetes at younger ages [1]. Patients with type 2 diabetes have an increased risk of cardiovascular complications [2]. These complications reflect a high burden for health and cause substantial costs related to diabetes [3–5]. Statins are lipid-lowering drugs that have been shown to reduce the risk of cardiovascular and cerebrovascular events in patients with diabetes [6–8]. After 2006, the Dutch guidelines for diabetes and cardiovascular risk management changed and recommended statin treatment for the prevention of cardiovascular events for practically all patients with type 2 diabetes, unless they have a low cardiovascular risk [9,10]. Although risk tables changed in recent guidelines, it was found using different risk calculation methods that few patients with type 2 diabetes are at such low risk [11]. Also, in other countries, statin treatment is recommended for a large proportion of the diabetes population [12,13].

Previous pharmacoeconomic analyses on the primary prevention of cardiovascular and cerebrovascular events estimated that statin treatment is likely to be cost-effective in patients with type 2 diabetes [14–16]. These pharmacoeconomic results, however, are limited because they made use of data from the same clinical trial, which included a restricted patient population with high adherence levels. Adherence to statins is a well-known problem in clinical practice [17,18], and therefore important to take into account when assessing cost-effectiveness. Furthermore, attention should be paid to the risk level where treatment becomes cost-effective. Greving et al. [19] recently demonstrated for a hypothetical primary prevention population that statins were not cost-effective in persons at low risk in The Netherlands. Whether this may also be true for patients with type 2 diabetes at relatively low risk is not known. Earlier detection of type 2 diabetes and younger age of these patients cause that patients with lower risk for cardiovascular and cerebrovascular events are being identified and treated with statins [20]. For better guidance on treatment decisions, it is important to gain an insight into the cost-effectiveness of statin treatment in patients with type 2 diabetes using the cardiovascular risk estimates and adherence levels based on patient data from actual practice.

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The objective of this study was to determine whether statin treatment for primary prevention, started at the time of diagnosis of type 2 diabetes, is cost-effective from a health care payers' perspective in The Netherlands, taking nonadherence, baseline risk, and age into account.

Methods

Markov Model

The cost-effectiveness of statin treatment for primary prevention, started at the time of type 2 diabetes diagnosis, was determined with a Markov model (Fig. 1). A population with statin treatment and a population without the use of any lipid-regulating treatment were simulated with the model. The design of the model was the same for both populations, with only probabilities of transitions to events changed by the use of statin treatment. We assumed that all patients got optimal secondary prevention. Differences in costs and effects were evaluated.

Because we aimed to determine the cost-effectiveness of primary prevention, all patients started in the "otherwise healthy" state, that is, patients with type 2 diabetes having experienced no previous cardiovascular or cerebrovascular event. Ten different health states were included in the Markov model, and patients could shift to another health state after a 1-year cycle, for which half-cycle corrections were performed [21]. The adverse events rhabdomyolysis and myopathy were taken into account. Patients who had experienced an adverse event returned to the otherwise healthy state in the next run. The correction for patients discontinuing treatment because of adverse events was done by applying real-world adherence rates, which include patients who have stopped statin treatment after an adverse event. In the base case, a time horizon of 10 years was used, because we were focusing on primary prevention.

Event Probabilities

Probabilities of shifting to an event state were taken from results of the United Kingdom Prospective Diabetes Study (UKPDS) risk engine, with which the annual rates for an event over a 10-year period can be calculated (see below) [22–24]. When patients experienced a nonfatal event in the model, they moved to the "postevent" state in the next cycle. All patients in the cohort experienced age-specific probabilities of dying from other causes. These probabilities were taken from the Dutch lifetime tables, taking the ageing of the Dutch population explicitly into account [25]. Because we evaluated primary prevention, we used a simplified adjustment on the death rate after the occurrence of an event. That is, for patients in postevent states, the probabilities of death, taken from Dutch lifetime tables, were increased twofold based on previous studies [26,27].

The UKPDS risk engine was used to estimate the patients' 10-year risks for coronary heart disease (CHD) and stroke on the basis of patient characteristics, including age, lipid ratio, and other risk factors [22–24]. These patient characteristics were obtained from the Groningen Initiative to Analyse Type 2 Diabetes Treatment (GIANTT) database. The GIANTT database contains anonymised longitudinal information retrieved from electronic medical records of general practitioners and is maintained by the University Medical Center Groningen [28]. Information on age, lipid ratio, and smoking status was taken at the time of type 2 diabetes diagnosis, in line with Dutch guidelines that advise statin treatment for patients with type 2 diabetes immediately after diagnosis for practically all patients [9,10]. Because it is to be expected that hemoglobin A_{1c} and blood pressure values will decrease after diagnosis because of the initiation of glucose-lowering and blood pressure–lowering treatment, we averaged the values for hemoglobin A_{1c} and systolic blood pressure at 1 and 2 years after the diagnosis for estimating the 10-year risks. In this way, we aimed to estimate the risk factor levels achieved with such treatment and assumed that patients remain adequately treated for these other risk factors during follow-up. This allowed us to assess the risk reduction of statin treatment in addition to the risk reduction caused by concurrent treatment for the other risk factors. Clinical data retrieved from the GIANTT database for a cohort of patients diagnosed with type 2 diabetes in 2007, 2008, or 2009 were inserted into the UKPDS risk engine. Patients with a history of CHD or stroke (International Classification of Primary Care codes K75, K76, and K90) [29] or who had a prescription for any lipid-regulating treatment (Anatomical Therapeutic Chemical (ATC) C10) [30] during the year before diagnosis were excluded.

In total, 4683 patients with newly diagnosed type 2 diabetes without a history of cardiovascular and cerebrovascular events were extracted from the GIANTT database and included in the UKPDS risk engine. The average patient was aged 61.3 years, and there were slightly more women than men (51.4%). On average, patients had a hemoglobin A_{1c} level of 6.7%, systolic blood pressure of 140 mm Hg, and a lipid ratio of 5 (total cholesterol/high-density lipoprotein cholesterol); 18% of the patients were smokers; and 1.6% had atrial fibrillation according to their medical records.

The average 10-year risk of the population aged 25 to 65 years at type 2 diabetes diagnosis was 16% for CHD, 8% for fatal CHD, 4% for stroke, and 0.7% for fatal stroke. Stratifying the 10-year

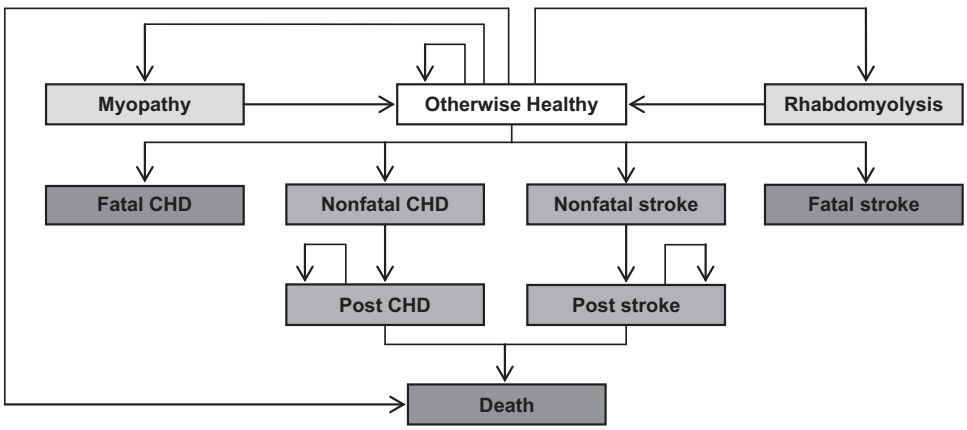

Fig. 1 – Markov model. CHD, coronary heart disease.

Table 1 – Incidence, effectiveness, disutilities and cost data for the base case.

Parameter	Base case	Distribution	Data source	Reference
Annual risks				
CHD yearly risk, % (10-year risk)	1.7, 1.8, 1.9, 2.0, 2.0, 2.1, 2.2, 2.3, 2.4, 2.5 (21%)	Beta	Real world data from GIANTT database inserted in UKPDS risk engine	-
Fatal CHD yearly risk, % (10-year risk)	0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6 (11%)	Beta	Real world data from GIANTT database inserted in UKPDS risk engine	-
Stroke yearly risk, % (10-year risk)	0.3, 0.4, 0.4, 0.5, 0.6, 0.6, 0.7, 0.8, 0.9, 1.0 (6%)	Beta	Real world data from GIANTT database inserted in UKPDS risk engine	-
Fatal stroke yearly risk, % (10-year risk)	0.1, 0.1, 0.1, 0.1, 0.1, 0.1, 0.1, 0,1, 0.2, 0.2 (1%)	Beta	Real world data from GIANTT database inserted in UKPDS risk engine	-
Myopathy (per 100,000 person years)	11	Beta	Systematic review	31
Rhabdomyolysis (per 100,000 person years)	3	Beta	Systematic review	31
Overall mortality rate (10-year risk)	12%	-	Actual rates	25
Statin treatment effectiveness (relative risk)				
MI	0.69	Lognormal	Meta-analysis	8
Stroke	0.70	Lognormal	Meta-analysis	8
Mean adherence rate				
First year	81%	Beta	Real world data from the IADB.nl prescription database	-
Second year	77%	Beta	Real world data from the IADB.nl prescription database	-
Third until tenth year	75%	Beta	Real world data from the IADB.nl prescription database	-
Disutility				
MI	0.06	Triangular	Meta-analysis	37
Stroke	0.22	Triangular	Meta-analysis	37
Act of taking statin	-0.001	Triangular	Assumption	38,39
Annual cost data (€)				
Statin treatment				
Simvastatin 40 mg	€ 7.30	-	Official tariff	40
Doctor visits	€ 59.5	-	Official tariff	41
Laboratory fee	€ 20.3	-	Official tariff	42
Pharmacists fee	€ 24.3	-	Official tariff	43
Myopathy	€ 59.5	Gamma	Assumption	-
Rhabdomyolysis	€ 11,126	Gamma	Cost study	44
MI				
First year	€ 5,012	Gamma	Cost study	45
Subsequent years	€ 1,885	Gamma	Cost study	5
Stroke				
First year	€ 13,480	Gamma	Cost study	46
Subsequent years	€ 1,885	Gamma	Cost study	5
Death	€ 2,902	Gamma	Assumption	19

CHD, coronary heart disease.

cardiovascular risks by age showed that age has a large effect on the risk. Patients aged 56 to 65 years at diagnosis of type 2 diabetes had an average risk of 21% for CHD, 11% for fatal CHD, 6% for stroke, and 1% for fatal stroke, and patients aged 46 to 55 years had risks of 15%, 6%, 3%, and 0.4%, respectively. Patients aged 36 to 45 years were estimated to have an average risk of 9% for CHD, 3% for fatal CHD, 1% for stroke, and 0.1% for fatal stroke.

Statin Treatment and Adherence

Statin efficacy was modeled by implementing the relative risk reduction found in a recent meta-analysis of randomized clinical trials on the primary prevention of cardiovascular and cerebrovascular events in patients with diabetes with statins [8]. Overall relative risk reductions of 31% for nonfatal CHD and fatal CHD and 30% for nonfatal stroke and fatal stroke were applied. The risks for adverse events myopathy and rhabdomyolysis were taken from a systematic review [31].

Adherence to statins was modeled by using real-world data from the IADB.nl database, which is a pharmacy research database in The Netherlands with a sample of the Dutch population of 500,000 persons. Patients with type 2 diabetes and no history of cardiovascular and cerebrovascular events were identified by the use of medication proxies (Appendix I). Statin adherence rates were defined as the percentages of pill days covered (PDC) [32]. Adherence rates were measured for patients starting statin treatment from 2008 up to and including 2010 (ATC C10AA, C10BA, and C10BX). Patients were considered as a starter of statin treatment when they did not use any lipid-lowering medication (ATC C10) in the year before the start of the statin treatment. Adherence rates were measured up to a maximum of 3 years, and in the base case

Table 2 – One-way sensitivity analyses (base case values between brackets).

Assumption	Cost-effectiveness
Base case	€2,245
Statin costs (€7.3)	
€18.5 (actual costs IADB.nl population)	€2,644
€50	€3,766
€100	€5,547
Myopathy (11 op 100.000 years)	
100	€2,247
Discounting rate (effects 1.5%;costs 4%)	
Effects 3%; costs 3%	€3,041
Effects 4%; costs 4%	€3,144
Disutility taking a pill (0.999)	
No disutility	€2,155
Time horizon (10 years)	
5 years	€12,424
Adherence rate (81%, 75%, 77% respectively first, second and subsequent years)	
Full adherence (80-100% PDC) in all years	€1,534
50% adherence in all years	€3,312
Adherence decreasing 2% each year after year 3	€2,266
Adherence decreasing 5% each year after year 5	€2,297
Relation statin efficacy and non-adherence (≥80%=1;20-80%=linear;≤20%=0)	
≥70%=1;30-70%=linear;≤30%=0	€2,217
≥80%=1;0-80%=linear	€2,175
≥60%=1;0-50%=linear	€2,108
UKPDS risk overestimation	
Lowering risk with 50%	€6,500

we assumed that statin adherence stayed constant after year 3, as was observed in a previous study [17].

Nonadherence was modeled by reducing the statin efficacy. Statin treatment with 80% or more PDC was assumed to be associated with full efficacy [33]. Patients with 20% or less PDC were assumed to be associated with no efficacy of the statin treatment. Efficacy of intermediary levels of PDC was approximated with linear interpolation in the base case because studies indicate that there is a linear association between adherence levels and reductions in low-density lipoprotein cholesterol and in hospitalizations [34–36].

In 1660 patients who started statin treatment, the mean PDC was 81% during their first year of statin use. Adherence rates decreased to 77% and 75% in year 2 and 3, respectively. In total, 1049 patients were followed for at least 2 years and 479 for 3 years. Because we allowed new users to be included during the study period, some patients could be followed only for 1 year. The decrease in the number of patients in the follow-up years was mainly due to later inclusion into the study rather than early dropout.

Health Effects and Costs

We determined the difference in quality-adjusted life-years (QALYs) between no lipid-regulating treatment and treatment with a statin. QALYs were calculated by multiplying the time in a specific health state with the quality of life associated with the health state. For patients experiencing a CHD or stroke, disutility scores were 0.06 and 0.22, respectively [37]. These utility scores were constant over time. A small disutility of 0.001 for taking a statin pill every day was included [38,39].

All cost estimates were updated to 2012 euros with the Dutch consumer price indices (http://statline.cbs.nl). Annual costs for statin treatment in the base case were based on statin pill costs (€7.3 for 40 mg generic simvastatin) [40], two GP visits (€59.5) [41],

Table 3 – Outcomes of the cost-effectiveness analysis stratified by age and risk for CHD and stroke

Age (y)		10-y risk for CHD; fatal CHD; stroke; fatal stroke	Proportion per age group	QALYs 1,000 patients	Costs per 1,000 patients (€)	Cost-effectiveness
<45*	1.	3; 1; 1; 0	27.5	−8	814,012	Inferior†
	2.	6; 1; 1; 0	28.5	−3	789,256	Inferior†
	3.	9; 3; 1; 0	21.8	11	738,926	€66,537‡
	4.	13; 4; 2; 0	9.5	43	689,576	€16,085§
	5.	16; 6; 3; 1	12.7	77	634,993	€8,223§
45–55‖	1.	6; 2; 1; 0	21.1	9	758,216	88,440†
	2.	10; 4; 2; 0	28.7	49	674,895	€13,828§
	3.	15; 6; 3; 0.5	20.8	75	623,327	€8,345§
	4.	20; 7; 4; 0.5	16.7	96	559,641	€5,810§
	5.	26; 10; 5; 1	12.6	145	486,131	€3,353§
55–65¶	1.	6; 3; 3; 1	6.8	43	638,881	€14,824§
	2.	10; 4; 3; 1	30.4	61	618,594	€10,119§
	3.	21; 11; 6; 1	34.7	193	432,890	€2,245§
	4.	27; 13; 7; 1	15.9	197	382,633	€1,939§
	5.	35; 24; 9; 2	12.3	453	276,148	€609§

Note. inferior = no cost-effectiveness is calculated because of the negative effect on QALYs. CHD, coronary heart disease; QALY, quality-adjusted life-year.

* Weighted cost-effectiveness for treating all patients with diabetes younger than 45 years in The Netherlands = €57,244.

† >€80,000.

‡ €50,000–€80,000.

§ <€20,000.

‖ Weighted cost-effectiveness for treating all patients with diabetes between 45 and 55 years in The Netherlands = €8,295.

¶ Weighted cost-effectiveness for treating all patients with diabetes between 55 and 65 years in The Netherlands = €2,480.

#€20,000–€50,000.

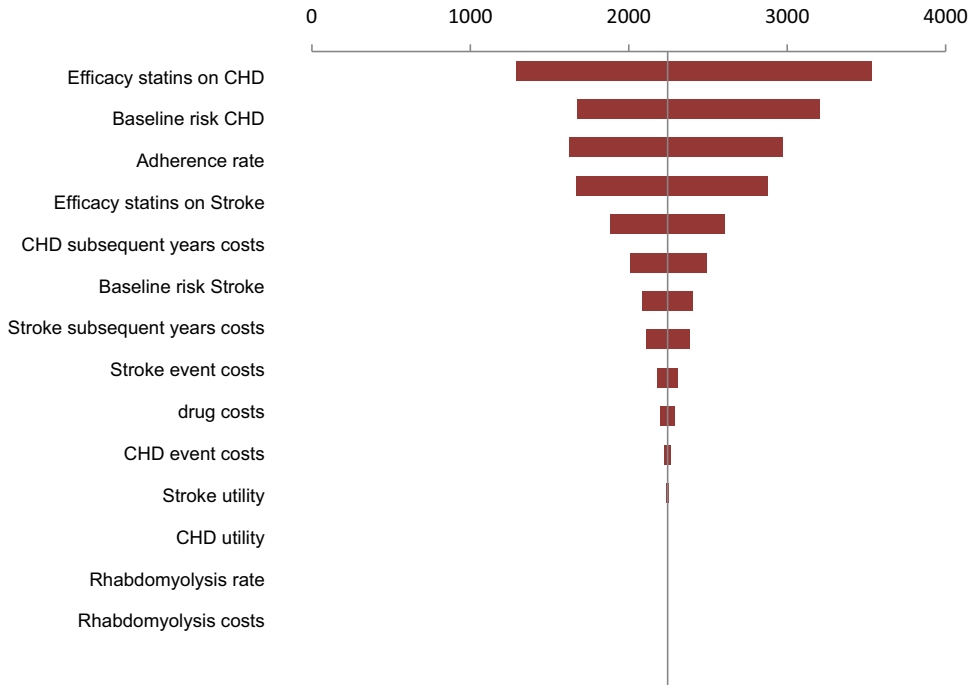

Fig. 2 – Tornado diagram; all parameters are increased and decreased with 25%. CHD, coronary heart disease.

annual lipid spectrum testing (€20.3) [42,44], and four pharmacists' prescription fees (€23) [43]. Event costs were based on the literature (Table 1).

Economic Analysis

The model was run over a time horizon of 10 years. Costs were discounted at 4% and health effects at 1.5%, following the Dutch guidelines [41]. In the base case, a 60-year-old patient was assessed, based on the average age of 61.3 years at type 2 diabetes diagnosis in the GIANTT database population. Mean 10-year cardiovascular risks of patients aged 56 to 65 years at type 2 diabetes diagnosis were used. With the use of a tornado diagram, the effect of the parameters on the outcome of the cost-effectiveness was assessed. In addition, the effects of age and baseline risk for CHD and stroke were evaluated. To assess the effect of individual parameters that may vary between countries or that were based on assumptions, one-way sensitivity analyses were performed. This included sensitivity analyses for statin costs, adverse event rates, discounting rates, disutility of taking a pill every day, time horizon, adherence rates, and relation between nonadherence and efficacy. Parameter variations tested are presented in Table 2. We also included a one-way sensitivity analysis to account for the possible overestimation by using the UKPDS risk engine, assuming a maximum reduction of 50% in the estimates [47]. Finally, a probabilistic sensitivity analysis with 5000 iterations was performed to deal with parameter uncertainty [48]. The parameter distributions used are listed in Table 1.

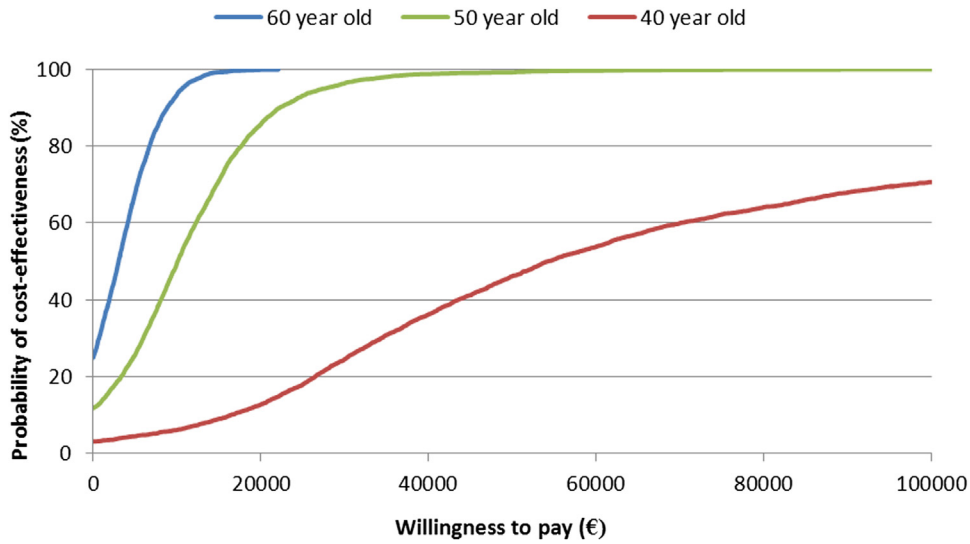

Fig. 3 – Cost-effectiveness acceptability curves from the probabilistic sensitivity analysis.

Results

Economic Analysis

In the base case, cost-effectiveness is €2245 per QALY (Table 2). Sensitivity analyses were performed to investigate differences in risks for CHD and stroke according to age. In Table 3, the outcomes of the cost-effectiveness analysis are shown stratified by age and 10-year risks for CHD and stroke. The risks chosen for each age group were based on actual risk ranges within the GIANTT database population. Treating all type 2 patients younger than 45 years for primary prevention of cardiovascular and cerebrovascular events was not cost-effective, with costs of €57,243 per QALY. Treating all patients aged 45 to 55 years at diagnosis was cost-effective, with costs of €8295 per QALY. For 21.1% of the patients, however, cost-effectiveness would be high and not cost-effective (Table 3).

The tornado diagram (Fig. 2) shows that the efficacy of the statins, the baseline risk for CHD and stroke, and the adherence rates have a large effect on the outcome of the cost-effectiveness. In the one-way sensitivity analyses (Table 2), statin costs also have a major effect on the cost-effectiveness. In The Netherlands, statin costs for 40 mg generic simvastatin were only €7.3 annually. The actual annual statin costs per patient in the IADB.nl population were €18.5, which results in a negative effect on cost-effectiveness (€2644 per QALY). Changing the time horizon to 5 years will lead to a substantial increase in costs (€12,424 per QALY). Increasing adherence to statin treatment will improve cost-effectiveness. Full adherence reduces the costs to €1534 for the base case. However, changing the assumptions on the adherence rate after year 3 does not have a great effect on cost-effectiveness (Table 2).

The acceptability curves of the probabilistic sensitivity analyses in Figure 3 show that the probability that statin treatment is cost-effective for the average 60-year-old patient is 100%, using a threshold of €20,000 per QALY. Considering the average 40-year-old patient, the analysis shows that with this threshold of €20,000 per QALY, the probability that it is cost-effective is less than 15% (Fig. 3).

Conclusions

We estimated that statin treatment for primary prevention starting at the time of diagnosis of type 2 diabetes is cost-effective at €2245 per QALY in the base case. There is great diversity in the risks for CHD and stroke in the type 2 diabetes population. Differences in age and 10-year risks for CHD and stroke result in large differences in cost-effectiveness from losing QALYs to being almost cost neutral. With the adherence rates seen in practice, it can be concluded that treating all patients younger than 45 years with type 2 diabetes at diagnosis with statins for primary prevention is not cost-effective. For patients aged between 45 and 55 years at diagnosis, statin treatment is cost-effective except when the 10-year risk for CHD is as low as 6%. For the other patients, statin treatment is expected to be cost-effective.

Our finding that statin treatment for primary prevention is cost-effective for the average 60-year-old patient is in line with other pharmacoeconomic analyses [14–16]. The finding that statin treatment is not cost-effective in patients at low risk is in line with findings from Greving et al. [19]. Cost-effectiveness, however, appears slightly better in our diabetes population. For a 65-year-old patient with a 10-year risk of 15%, Greving et al. estimated the costs at €12,652 per QALY whereas we estimated the costs at €10,119 per QALY for a 60-year-old patient with a 10-year risk of 13%.

Currently, there are more than 800,000 patients with diabetes in The Netherlands [49]. Within the GIANTT database population, 14% of the patients have a cardiovascular history, implying that 688,000 patients might be eligible for primary prevention with statin treatment. With the current price levels, such statin treatment would cost the Dutch health care system around €75.7 million each year. The broad range for cost-effectiveness between the individual patients suggests that the efficiency of the treatment could be increased by focusing on patients with higher cardiovascular risk and higher ages. Within the GIANTT database primary prevention population, 19% of the patients had an age at diagnosis of less than 50 years in whom starting statin treatment at the time of diagnosis may not be cost-effective.

Cost-effectiveness was assessed taking various parameters into account, such as adherence and adverse events. Adherence to statin treatment obviously plays an important role in cost-effectiveness analysis. In our study population, adherence rates for statin treatment were higher than reported in other studies [17,50]. Nevertheless, further improving adherence would lead to improvements in cost-effectiveness. Furthermore, in the base-case analysis, the statin costs of 40 mg generic simvastatin (€7.3) were applied; use of the average annual costs of statin treatment from the IADB.nl population (€18.5) has a minor negative effect on cost-effectiveness. Dutch guidelines [9,10] recommend 40 mg simvastatin or 40 mg pravastatin (€16.10) when statin treatment is started. Treating patients with 40 mg simvastatin has beneficial effects on cost-effectiveness. Nevertheless, some patients need a switch to more expensive statins to reach lipid goals [51]. In the base-case analysis, we chose a time horizon of 10 years. Shortening the time horizon to 5 years clearly affects the cost-effectiveness, indicating that primary prevention with statins is especially beneficial in patients with diabetes who can and will take the treatment for a longer period.

Strengths

We analyzed the baseline risk of a population of patients with type 2 diabetes using observational patient data that were inserted into the UKPDS risk engine. Because the GIANTT database cohort includes an unrestricted population of patients with type 2 diabetes in primary care, these data better reflect the population treated with statins in actual practice as compared to the patients included in trials. Adherence rates were also measured in the actual population. Both populations were taken from the Northern part of The Netherlands. Using the tornado diagram, the parameters that have a large effect on the outcome of the cost-effectiveness analysis—such as the efficacy of statins, the baseline risk for CHD and stroke, and adherence rates—were analyzed in detail. From this, it becomes clear that the utilities and the drug costs did not have a large effect on the results. The strength of this study is that we stratified the patients according to age. As a result of the broad ranges in the 10-year risks for CHD and stroke between the different age groups, broad variations in cost-effectiveness could be shown.

Limitations

First, the UKPDS risk engine was used for determining cardiovascular risks for patients with type 2 diabetes. There is evidence that the UKPDS risk engine overestimates the risks for CHD and stroke [47,52]. As shown in the sensitivity analysis, the costs per QALY could more than double when risks are overestimated by a factor of 2. It seems, however, that at the risk levels seen in the primary prevention diabetes population, the overestimation is probably not that high [47]. Second, adherence rates of the patients were measured in a pharmacy research database in which the indication of the patient was not known. Medication proxies had to be used for identifying diabetes primary prevention patients. The proxy for diabetes is known to give a high sensitivity [53]. The proxy for primary prevention showed a high

sensitivity of 85%. Around 15% of the included patients, however, can be expected to be secondary prevention patients. Third, the adherence rates were measured only for the first 3 years and assumed to stay constant over time afterwards. In addition, for the intermediate adherence levels, we assumed a linear relation with the efficacy. Although there is some evidence that these assumptions are acceptable [17,34–36], we tested them in the sensitivity analyses, which showed that various changes in the assumptions did not have much effect on the results. We used real patient data for the risk estimation and adherence rates, but treatment efficacy, disutilities, and cost data were based on literature. For statin efficacy as well as for post–myocardial infarction and poststroke utilities, we made use of estimates from meta-analyses, which applied minimum criteria for including appropriate data. For costs, we tried to retrieve the most recent data available but had to rely on multiple sources published in the past decade. Only direct health care costs were included. Including indirect costs would obviously be favorable for cost-effectiveness [45,46].

This study is an illustration for The Netherlands. In The Netherlands, statin costs are very low, and such medication is reimbursed for all patients. Other countries may have higher statin costs or higher nonadherence rates due to patient copayments, and cost-effectiveness might be less favorable. The population used in this analysis was from the northern part of The Netherlands, which is known to have a lower rate of immigrants and a lower socioeconomic status in comparison to other parts of The Netherlands [54,55]. As one could speculate that this might affect the estimated risks for cardiovascular events and the adherence rates in opposite directions, it is not clear to what extent this would result in relevant changes in our findings.

We used a time horizon of 10 years with cycle lengths of 1 year. Because of data availability, it was not possible to shorten the cycle length but by performing half-cycle corrections, the effect of this longer cycle length was minimized. Because we aimed to assess the effect of primary prevention of cardiovascular and cerebrovascular events, we did not perform a lifetime analysis but did shorten the time horizon in the sensitivity analysis to 5 years.

In general, primary prevention with statin treatment at the time of diagnosis is not cost-effective for all patients with type 2 diabetes. In the recent Dutch guidelines for cardiovascular management, 40 years is mentioned as the age limit for patients with diabetes below which statin treatment would seldom be indicated [9]. Our study indicates that this age limit may be set higher because, on average, starting statin treatment in patients younger than 45 years is not expected to be cost-effective. However, our results indicate that statin treatment, even with the levels of nonadherence and variations in choice of statin seen in actual practice, is highly cost-effective for patients older than 55 years at diagnosis with a time horizon of 10 years. Although it is acknowledged that there is no single treatment appropriate for all patients and the individual risk profile of a patient should be considered, these simple age-based recommendations could be helpful for guiding practice.

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Supplemental Materials

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